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International Congress on Ultrasonics, Universidad de Santiago de Chile, January 2009

Pulse subtraction Doppler

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Abstract

Recent advances have demonstrated the feasibility of molecular imaging using targeted microbubbles and ultrasound. One technical challenge is to selectively detect attached bubbles from those freely flowing bubbles and surrounding tissue. Pulse Inversion Doppler is an imaging technique enabling the selective detection of both static and moving ultrasound contrast agents: linear scatterers generate a single band Doppler spectrum, while non-linear scatterers generate a double band spectrum, one being uniquely correlated with the presence of contrast agents and non-linear tissue signals. We demonstrate that similar spectra, and thus the same discrimination, can be obtained through a Doppler implementation of Pulse Subtraction. This is achieved by reconstructing a virtual echo using the echo generated from a short pulse transmission. Moreover by subtracting from this virtual echo the one generated from a longer pulse transmission, it is possible to fully suppress the echo from linear scatterers, while for non-linear scatterers, a signal will remain, allowing classical agent detection. Simulations of a single moving microbubble and a moving linear scatterer subject to these pulses show that when the virtual echo and the long pulse echo are used to perform pulsed Doppler, the power Doppler spectrum allows separation of linear and non-linear moving scattering. Similar results are obtained on experimental data acquired on a flow containing either microbubble contrast agents or linear blood mimicking fluid. This new Doppler method constitutes an alternative to Pulse Inversion Doppler and preliminary results suggest that similar dual band spectra could be obtained by the combination of any non-linear detection technique with Doppler demodulation.

Keywords: microbubbles; pulse subtraction; Doppler; targeted contrast agents; pulse inversion

1. Introduction

One main challenge in targeted imaging is the development of sensitive imaging methods able to detect and distinguish adherent targeted contrast agents from the high background signal from freely circulating agents and tissue [1]. One potential detection method is Pulse Inversion Doppler (*PID*), developed by Simpsons et al [2]. This approach is able to separate linear moving scatterers from non-linear moving scatterers. By sending a Doppler sequence of N pulses at a pulse repetition frequency *PRF* and each pulse being an inverted copy of the previous one, and after Doppler processing the received echoes, signals arising from linear and non-linear moving scatterers are

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represented in different frequency bands in the calculated Doppler spectrum: the Doppler shifts due to the scattered odd harmonics such as the fundamental frequency and the 3rd harmonics will be represented in the $[-PRF/2 - PRF/4] \cup [PRF/4 PRF/2]$ region and the Doppler shifts due to the even harmonics will be represented in the remaining region: $[-PRF/4 PRF/4]$, provided the revised Nyquist limit (1) is respected for the scatterer velocities, where $f_{d,max}$ represents the maximum detectable Doppler shift.

$$f_{d,max} \leq PRF / 4 \quad (1)$$

In this paper we will describe a new imaging sequence, Pulse Subtraction Doppler (*PSD*). This is based on Pulse Subtraction, a contrast agent detection method introduced by Borsboom et al [3], using the difference in responses between tissue and contrast agents to enable a suppression of tissue signal and therefore increasing the contrast to tissue ratio (*CTR*). This paper investigates the possibility of using Pulse Subtraction signals in Doppler mode and tests the potential for using it as an alternative to *PID*, as the new technique also allows an easier scanner implementation, by using driving pulses having all the same phase. In the first part of this paper *PSD* will be explained as well as a description of the simulation and experimental studies conducted. In the second part the results of the studies will be given with some discussion and conclusions.

2. Methods

2.1. Pulse Subtraction Principle

Pulse Subtraction is based on the following multipulse sequence: A first short pulse p_1 followed by a second longer pulse p_2 made of the combination of multiple, time-shifted copies of the shorter pulse, as shown in (2), where for a given pulse p_1 , a second pulse p_2 is composed with T , being the length of p_1 and N the number of p_1 pulse copies.

$$\begin{cases} p_1(t) \\ p_2(t) = \sum_{n=1}^N p_1(t - nT) \end{cases} \quad (2)$$

An example of p_1 and p_2 is shown in the left column of Fig. 1.

As the difference in the pulses length generates echoes improper for comparison and processing, a “virtual” echo E_V has to be constructed accordingly to p_2 generation, as expressed in, (3).

$$\begin{cases} E\{p_1\} \\ E\{p_2\} = E\left\{\sum_{n=1}^N p_1(t - nT)\right\} \\ E_V = \sum_{n=1}^N E\{p_1\}(t - nT) \end{cases} \quad (3)$$

$E\{p_1\}$ is the echo acquired from p_1 and $E\{p_2\}$ the echo from p_2 . Both echoes and the virtual echo E_V are represented for linear and non-linear scattering in the middle and right column respectively in Fig. 1.

Subtracting the virtual echo from the long echo will remove linearly scattered signals. However for a non-linear system, such as contrast agent scattering, a signal will remain after subtraction. The response of a microbubble being

non-linear, it will respond differently in phase to a short or a long excitation. Both residues for linear and non-linear scattering are represented at the bottom of Fig.1.

The phase changes introduced by excitation pulses of different lengths suggest that *PSD* will provide the same type of information as obtained from *PID*.

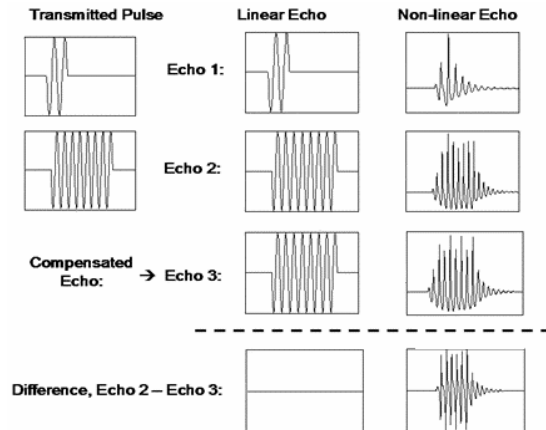


Fig.1 Principle of Pulse Subtraction using a 2 cycle incident pulse and an 8 cycle incident pulse. The amplitudes in the vertical axes and the time on the horizontal axes are all scaled

2.2. Pulse Subtraction Doppler Principle

For Pulse Subtraction Doppler, a series of N pulses is sent along a single line of sight, alternating a short pulse and a long pulse at a fixed *PRF*. Before conventional Doppler processing is applied, the compensation process described in (3) is performed on the N echoes. For echoes resulting from linear scatterers, they will be equivalent to echoes originating from normal pulsed Doppler, all the lines being identical for a non-moving linear target. However for non-linear scatterers, the Doppler data not being identical for successive pulses may introduce nonlinearities in the Doppler spectrum. A series of simulations and experiments were carried out to demonstrate the validity of the new technique.

2.3. Simulations

A simulation study was conducted to assess *PSD*. A modified Rayleigh-Plesset equation [4] was used to simulate the acoustic response of a microbubble to the Doppler pulse sequences. The transmitted pulse sequences consisted of 30 driving pulses, alternating between one short 2 cycle sine wave p_1 , and one long 8 cycle sine wave p_2 . Both pulses had a centre frequency of 2 MHz and a peak-negative pressure of 100 kPa. The *PRF* of the pulse sequences was 7 kHz. A virtual echo was then created, using the same adjusting parameters as for the construction of p_2 . The long echo and the virtual echo were used to simulate *PSD* data from a moving non-linear scatterer. A moving linear scatterer was also simulated for comparison.

2.4. Experiments

In vitro experiments were designed in order to assess *PSD* as a technique for separating moving linear scatterers from moving non-linear scatterers. A steady flow phantom was prepared on which Doppler data was acquired. A

blood mimicking solution [5] was used as a linearly scattering fluid and a solution of water and Sonovue (Bracco ResearchTM) contrast agents was used as a non-linearly scattering fluid. The fluid was pumped out of a glass container and the flow velocity adjusted via a rotameter. The PVC tubes used for the fluid transport were connected to a thin latex tube of low wall-attenuation, positioned in a water bath at the focus of a linear probe of an UltrasonixTM RP 500 research scanner. The probe was mounted in the water bath and used for firing the predefined Doppler pulse sequence and receiving the echoes. The Doppler M-mode pulse sequences were programmed on the scanner via MatlabTM and the echoes received were post-processed with MatlabTM to obtain the Doppler spectrums for the two different kinds of fluids. The central frequency of the transmitted pulses was 5MHz. The maximum MI was 0.4, and the length of pulse p_2 was two times that for p_1 .

3. Results

The upper figures in Fig.2 show the simulated *PSD* spectrums for a linear moving scatterer (a) and for a non-linear moving microbubble (b). The Doppler spectrums from the experimental data for a steady flow of linear blood mimicking fluid (c) and a solution of microbubbles (d) in the bottom figures have similar shapes as for the ones in the simulations. On a flow containing linear scattering, only one frequency shift, f_d , proportional to the velocity of the scatterer is being observed confirming that Pulse Subtraction Doppler is equivalent to performing Pulsed Doppler in that case. However for a flow containing non-linear microbubbles the Doppler spectrum shows two different frequency shifts, one of them being only due to the non-linear properties of the scattering. This demonstrates that the non-linear scattering can be discriminated from the linear one and appears in a different frequency band of the spectrum.

These results demonstrate that *PSD* makes it possible to discriminate non-linear and linear moving scatterers as they appear in different frequency bands of the Doppler spectrum.

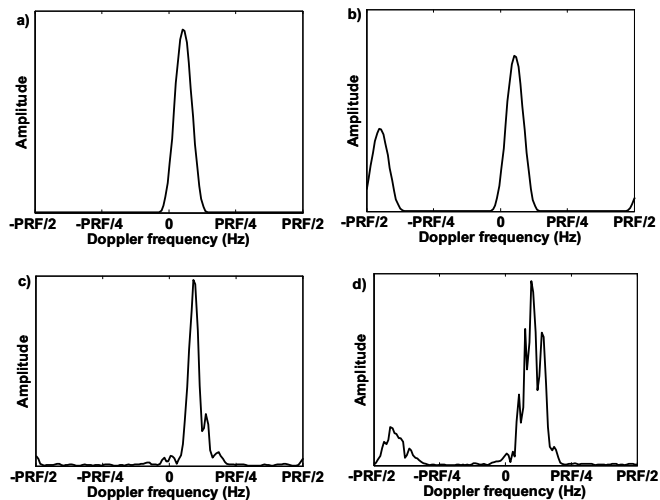


Fig.2 Pulse subtraction Doppler spectrums for a) simulated data of a linear moving scatterer, b) simulated data of a single moving microbubble, c) experimental data of a linear blood mimicking fluid, d) experimental data for a solution of microbubbles

4. Discussion and Conclusions

It has been shown that the signals issued from Pulse Subtraction can be used through Doppler processing to obtain dual band Doppler spectrums, allowing the detection and discrimination of non-linear moving scatterers from linear moving ones as they appear in different frequency bands of the spectrum. For *PSD* linear scattering will appear in the $[-PRF/4 \text{ } PRF/4]$ region and non-linear scattering in the remaining region of the spectrum, provided the revised Nyquist limit (1) is respected for the scatterer velocities.

It should be noted that this repartition is inverted compared to the *PID* spectrum. This is due to the fact that the transmitted pulses for *PSD* have all the same phase. Therefore for a linear target, Pulse Subtraction is similar to performing normal pulsed Doppler and for a non-linear target a supplementary phase shift of $PRF/2$ appears in the spectrum due to the relative change in phase of the echoes to a short or a long pulse. This technique potentially provides an easier implementation in scanners as it does not need phase inversion or amplitude modulation. Further research will look into the use of it for the detection of targeted microbubbles as well as the use of arbitrary sequences for non-linear Doppler with the objective of determining an optimised approach.

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